REMARKS/ARGUMENTS

Claims 5, 7, 10-13, 15-16 are pending in this application. Claims 1-4, 6, 8-9, and 14 have been previously canceled.

Claims 5, 10 and 15 have been amended herein to clarify that the method comprises inhibiting mycobacterial glutamine synthetase without causing significant toxic side effects in a mammal due to inhibition of mammalian glutamine synthetase. Claim 5 has been further amended to limit the R2 groups to methyl sulfoximine. The listing of R2 groups at the top of page 3 of this paper has been deleted as indicated by the brackets and strikethrough of the chemical structures. Claims 12 and 13 have been amended to correct the format of these multiple dependent claims. Claim 16 has been amended to correct dependency. No new matter has been introduced as a result of the claim amendments.

By the amendments, Applicants do not acquiesce to the propriety of any of the Examiner's rejections and do not disclaim any subject matter to which Applicants are entitled. *Cf. Warner Jenkinson Co. v. Hilton-Davis Chem. Co.*, 41 U.S.P.Q.2d 1865 (U.S. 1997).

Rejections under 35 U.S.C. §103

It is well established that a *prima facie* case of obviousness requires that the Office provide evidence to support three basic criteria: there must be some suggestion or motivation in the cited art to modify a reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Third, the prior art references must teach or suggest all the claim limitations. MPEP 2143.

Moreover, Office is respectfully reminded of the case law, namely, that there must be some prior art teaching which would have provided the necessary incentive or motivation for modifying the reference teachings. *In re Laskowski*, 12 U.S.P.Q. 2d 1397, 1399 (Fed. Cir. 1989); *In re Obukowitz*, 27 U.S.P.Q. 2d 1063 (BOPAI 1993) see also *Takeda Chemical Industries, Ltd. v. Alpharma Pty., Ltd.*, 492 F.3d 1350 (Fed. Cir. 2007).

The Office is respectfully reminded that for the 35 USC §103 rejection to be proper, both the suggestion of the claimed invention and the expectation of success must be founded in the prior art, and not Applicants' disclosure. *In re Dow*, 5 U.S.P.Q. 2d 1529, 1531 (Fed.Cir. 1988).

Claims 5, 7, 10-13, and 15-16 have been newly rejected under 35 USC §103(a) as being unpatentable over U.S. Patent No. 6,013,660, in view of Griffith et al. (Methods in Enzymology, 143:286-291, 1987) further in view of Harth et al. (J. Exp. Med. 189:1425-1435, 1999). Furthermore, the rejection of claims 5, 7, 10-13, and 15-16 under 35 USC §103(a) as being unpatentable over Harth et al. (J. Exp. Med. 189:1425-1435, 1999) in view of Griffith et al. (Methods in Enzymology, 143:286-291, 1987) has been maintained.

Applicants respectfully assert that the amended claims are non obvious in light of the cited prior art. Furthermore, the Office has made some factual errors in their arguments that the Applicants would like to address in addition to arguments traversing the rejections.

Claims 5, 10 and 15 have been amended to recite that the method of treating mycobacterial infections comprises administering a compound which inhibits mycobacterial glutamine synthetase (GS) without causing substantial toxic side effect as a result of substantially inhibiting mammalian GS and which inhibits the growth of a mycobacteria. Specifically, the claims have been amended in the preamble to read "[a] method for treating, palliating or inhibiting mycobacterial infections in a mammal by inhibiting mycobacterial glutamine synthetase without causing substantial toxic side effects in said mammal, said method comprising the steps of: . . ." Furthermore, the inhibiting step of claims 5, 10 and 15 has been amended to read "inhibiting the growth of a Mycobacteria species without causing substantial toxic side effects in said mammal."

The Office has rejected the claims as obvious primarily on the basis that similar compounds will have similar activities as noted in MPEP 2144 and quoted by the Office "[i]f such a species or subgenus is structurally similar to that claimed, its disclosure may

motivate one of ordinary skill in the art to choose the claimed species or subgenus from the genus, based on the reasonable expectation that structurally similar species usually have similar properties." However, this premise is based on the similarity or identity of the target in order to obtain similar properties. In the present claims, the target (mycobacterial GS) is not the same as the target in the prior art (mammalian GS). For certain proteins, sequence and structural homology are maintained across divergent species. In the case of glutamine synthetase this is not the case.

Applicants hereby submit a declaration under 37 CFR §1.132 from inventors Marcus A. Horwitz, M.D. and Owen W. Griffith, Ph.D. (see Appendix 1), demonstrating that significant sequence or structural homology does not exist between mammalian and mycobacterial species of GS. Firstly, only 74 (15.5%) of the 478 amino acids of *M. tuberculosis* GS are identical to mammalian GS and the similarity (identical + conservative changes) is only 30.8%. Second, mycobacterial GS comprises 12 subunits of a 478 amino acid polypeptide and mammalian GS comprises 8 subunits of a 373 amino acid polypeptide. Based on sequence and structural homology alone, a person of ordinary skill in the art would not consider these two enzymes substantially similar and would not expect any given compound to inhibit the two enzymes to substantially the same extent. Furthermore, the inventors present data on the inhibition of mammalian and mycobacterial GS activity and mammalian and mycobacterial γ-glutamylcysteine synthase activity by several different compounds in the declaration. Those data show that α-methyl-MSO and MSO are approximately equally effective as inhibitors of purified human GS, but α-ethyl-MSO is a very weak inhibitor of human GS (200 μM inhibits only 3%; Table 1 of the attached declaration). In contrast, α-ethyl-MSO is the most effective inhibitor of mycobacterial GS (2 μM inhibits 92%; Table 1). These results show (i) that in this series of compounds structurally similar isomers do not have predictably similar results (*e.g.*, α-methyl-MSO is a strong inhibitor of human GS; α-ethyl-MSO is a poor inhibitor), and (ii) given the results with human GS, the efficacy of α-ethyl-MSO as an extremely potent inhibitor of mycobacterial GS was unpredictable and unexpected in view of the weakness with which it inhibited mammalian GS.

Furthermore, this unexpected result is key to the success of the therapy since if α-ethyl-MSO was as weak an inhibitor of mycobacterial GS as it is of human GS, then the therapeutic dose would need to be much, much higher. Griffith has shown that at high doses α-ethyl-MSO causes convulsions (Griffith and Meister, Journal of Biological Chemistry 253:2333-2338, 1978). It was thus not obvious prior to the work leading to the instant application that α-ethyl-MSO could achieve an anti-mycobacterial effect at doses that were not toxic to the host animal.

Thus, within this genus even structurally related compounds cannot be expected to have predictable activity against even the same target enzyme. The compounds of the genus can certainly not be predicted to have similar activity against different target enzymes (*i.e.*, mycobacterial GS and mammalian GS) which lack significant sequence or structural homology.

Therefore, in this response the Applicant has identified each recitation of GS with an indication of its species. The species of GS in the prior art and in the instant specification and claims are different and the claims have been amended to clarify this point.

The '660 patent teaches methods of treating mammalian disease associated with infection by pathogenic mycobacteria comprising administering L-methionine-S-sulfoximine to the mammal. As stated by the Office on page 3, paragraph 3 of the Office Action mail November 7, 2007, "[t]he '660 patent does not expressly disclose the particular alpha-alkylated sulfoximines claimed herein."

Griffith et al. teaches alpha-ethyl-methionine-sulfoximine as an inhibitor of mammalian GS but Griffith does not teach or suggest that alpha-ethyl-methionine-sulfoximine inhibits mycobacterial GS and does not teach the unexpectedly high potency with which alpha-ethyl-methionine-sulfoximine inhibits mycobacterial GS.

Harth et al. teaches L-methionine-S-sulfoximine as an inhibitor of mycobacterial and mammalian GS and its ability to block growth of pathogenic mycobacteria in human monocytes.

As the Applicants noted above, mycobacterial GS and mammalian GS, are not substantially the same and compounds, even if structurally related, cannot be presumed to have predictable activity against enzymes which lack significant sequence or structural homology.

The Office cites *In re Dillon* and *In re Deuel* to support the assertion that structurally similar species have an expectation of having similar properties. However, this assertion is based upon the premise that the target of the structurally similar species is the same or similar. The currently pending claims require a target dissimilar to the prior art target. Structurally similar species cannot be expected to have similar properties against dissimilar targets.

Since the targets of the structurally similar compounds, mammalian GS and mycobacterial GS, are dissimilar, as discussed by the inventors in the 1.132 declaration attached hereto, the structural similarity of the compounds is not predictive of their activity against dissimilar targets. In fact, as discussed *supra* the α-ethyl-MSO was unexpectedly much more active against mycobacterial GS than against human GS.

The Office states on page 3, last paragraph of the Office Action dated November 7, 2007, that Griffith teaches that α-ethyl-methionine sulfoximine is a selective inhibitor of GS. The Office does not state whether the GS taught in Griffith is mammalian or mycobacterial. As discussed *supra*, this is a critical piece of information. The Office further defines the meaning of Griffith's statement by quoting Griffith as follows: "[s]elective inhibition of either glutamine synthetase or γ-glutamylcysteine synthetase is possible in vitro or in vivo using analogs of methionine sulfoximine." If the Office's conclusion that the compounds would behave similarly due to similarities in structure, all the α-alkyl-MSOs must also inhibit both enzymes, regardless of the dissimilarities of the target enzymes. As shown in Griffith (Figure 1), this is, in fact, not the case. Alpha-methyl-MSO does inhibit both species of enzymes but α-ethyl-MSO only inhibits the sheep brain GS, not rat kidney γ-glutamylcysteine synthetase.

The Office asserts on page 6, first paragraph of the Office Action dated November 7, 2007 that "[i]t would have been obvious to a person of ordinary skill in the

art at the time the invention was made to use α-ethylmethionine sulfoximine as an inhibitor of mycobacterial glutamine synthetase because the '660 patent discloses L-methionine sulfoximine as a selective inhibitor of glutamine synthetase and Griffith teaches that α-ethylmethionine sulfoximine is a selective inhibitor of glutamine synthetase. One having ordinary skill in the art would have been motivated [sic] employ particular alpha-alkylated compounds herein, because, '660 patent discloses suggests [sic] the use of analogues of methionine sulfoximine, and α-ethyl methionine sulfoximine, the compound instantly claimed, is a well known analogue of methionine sulfoximine known for its activity against glutamine synthetase." Applicants respectfully submit that a person having ordinary skill in the art would not have been motivated to combine the references because of the known differences in mycobacterial and mammalian GS and the previous showing that α-ethyl-MSO does not inhibit all enzymes that are inhibited by MSO (*e.g.*, it does not inhibit sheep brain γ-glutamylcysteine synthetase).

The basic factual inquiries laid out by the courts in Graham v. John Deere Co. include 1) determining the scope and content of the prior art; 2) ascertaining the differences between the prior art and the claims at issues; 3) resolving the level of ordinary skill in the pertinent art and 4) evaluating evidence of secondary considerations, i.e., objective indicia of unobviousness (commercial success, long felt but unresolved needs, failure of others, and unexpected results, among others). The instant inventors, in the attached declaration and original filing have cited two unexpected results of the compounds in the claimed methods. Firstly, α-ethyl-MSO and α-methyl-MSO did not predictably inhibit mycobacterial GS at levels expected from earlier results with mammalian GS. Secondly, α-methyl-MSO and α-ethyl-MSO were unexpectedly as effective as MSO against mycobacterial GS *in vivo* whereas those compounds were less effective against mammalian GS *in vivo* as judged by their weaker convulsant activity. Therefore, the observation of unexpected results, in addition to the other arguments presented herein, supports the non-obviousness of the pending claims over the cited prior art.

Furthermore, the Office assumes that, as a result of their assertion that structurally similar compounds have similar activity, α-alkyl MSOs which inhibit mycobacterial GS (which has been demonstrated by declaration as not predictable), will be effective anti-mycobacterial agents. This is not the case as demonstrated by the Office's cited reference Harth et al. Harth discloses phosphonothricin, a compound which is structurally similar to MSO and potently inhibits *M. tuberculosis* GS *in vitro* (Figure 1, page 1428 of Harth et al.) but does not have any effect on the growth of *M. tuberculosis* (Figure 2, page 1430). This example, in the Office's cited prior art, demonstrates that compounds that inhibit mycobacterial GS *in vitro* do not predictably inhibit the growth of mycobacteria.

Therefore, in light of the inventors' declaration under 37 CFR 1.132 and the arguments presented *supra*, the Applicants respectfully assert that the cited prior art do not disclose a method of treating mycobacterial disease by administering a mycobacterial GS inhibitor which does not cause substantial toxic side effects in mammals due to inhibition of mammalian GS and inhibits the growth of a mycobacteria pathogen. The combination of the '660 patent, Griffith, and Harth do not disclose the methods of amended independent claims 5 and 10, and the claims that depend therefrom. Therefore the Office has not established *prima facie* obviousness of claims 5, 7 and 11-13 over the '660 patent in view of Griffith et al. and further in view of Harth et al. Applicants respectfully request the withdrawal of the rejection on this basis.

Furthermore, Applicants assert that the combination of Griffith and Harth do not disclose the method of amended independent claims 5, 10 and 15. Therefore the Office has not established *prima facie* obviousness of claims 5, 7, 10-13, and 15-16 over Griffith et al. in view of Harth et al. Applicants respectfully request the withdrawal of the rejection on this basis.

Double Patenting

The rejection of claims 5, 7, 10-13, and 15-16 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2 of U.S.

Patent No. 6,013,660 in view of Griffith et al. (J. Biol. Chem. 1979, 1205-1210) has been maintained. Applicants respectfully traverse.

The Office has asserted on page 9, middle of third paragraph of the Office Action that "[o]ne of ordinary skill in the art would have reasonably expected that the instant compound, would have same or substantially similar beneficial therapeutic effects and usefulness in methods for treating, palliating or inhibiting mycobacterial infections in a mammal, based on the reasonable expectation that structurally similar species usually have similar properties." As Applicants have asserted in detail *supra* and in the attached declaration, structurally similar species cannot be expected to have similar properties against different target enzymes. Furthermore, among this genus of compounds, structurally similar species do not even have similar properties against the same target enzyme.

The Office further states in the sentence bridging pages 10 and 11 of the Office Action that "[t]he members of a homologous series must possess unexpected properties not possessed by the homologous compounds disclosed in the prior art. *In re Hass* 141 F.2d 127, 60 USPQ 548 (CCPA 1944)." As shown in the Declaration (Table 1) and discussed *supra* α-ethyl-MSO is unexpectedly efficacious against mycobacterial GS.

Furthermore, the Office stated that Applicants' previous arguments were found "unpersuasive since the compounds disclosed in the secondary reference are considered to have strong structural similarity with the sulfoximine compound claimed in the '660 patent as discussed above." (Page 11 of November 7 office action, last paragraph) Applicants respectfully assert that the compounds are not the same and that the target of the compounds is different. As discussed supra and in the attached declaration, mammalian GS and mycobacterial GS do not have substantial sequence and structural similarity and there can be no presumption of similar activity of different compounds against different target enzymes.

The claimed methods require compounds having activities not disclosed in either of the '660 patent or Griffith et al. Thus, the methods recited in claims 1 and 2 of the '660 patent do not read on the methods recited in claims 5, 7, 10-13 and 15-16 of the

instant application in view of the disclosure of Griffith et al. Additionally, there is nothing in the art that teaches or suggests that the methods claimed by the Applicants are equivalent to the methods claimed in the '660 patent. In order to fulfill the requirements of a double patenting rejection, the use of methods claimed in the '660 patent in view of Griffith et al. must be capable of infringing the Applicants' claims. The '660 patent claims do not contemplate use of a compound, such as an MSO analog, which inhibits mycobacterial GS while not substantially inhibiting mammalian GS and inhibiting the growth of a mycobacterial pathogen. Moreover, the Applicants' claims are not just obvious variations of claims 1 and 2 of the '660 patent that would extend the patent term of the '660 patent. Applicants respectfully request that the double patent rejection be withdrawn.

Conclusion

In light of the claim amendments and the arguments presented *supra*, Applicants respectfully assert that the pending claims are in condition for allowance and request that a timely Notice of Allowance be issued in this case.

The Commissioner is authorized to charge any fee which may be required in connection with this Amendment to deposit account No. 50-3207.

Respectfully submitted,

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